Keywords Rhodopsin/Antioxidant/Collagen/Scurvy/Vitamin A/Vitamin C

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In this article...

- The role vitamin A plays in vision, and the effects of deficiencies on ocular health and function
- How vitamin A maintains epithelial integrity and immune function
- The effect of vitamin C on collagen production and what causes scurvy

Vitamins A and C: their function and structure explained

Key points

Vitamin A is fat soluble and can be obtained directly or indirectly from food

A deficiency of vitamin A can cause night blindness

Humans cannot synthesise vitamin C so must obtain it directly from their diet

Vitamins A and C are essential for maintaining healthy skin and a healthy immune system

Chronic vitamin C deficiency may result in scurvy

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Abstract This first article in a series on the role of vitamins and minerals explains the structure and function of vitamins A and C, which are needed for healthy skin and a healthy immune system. Vitamin A is obtained pre-formed in food or synthesised by the body from beta-carotene, which is present in many coloured fruits and vegetables. It is essential to ocular health and function, and deficiencies are associated with night blindness. Vitamin C is water soluble and cannot be manufactured by the body. Dietary sources include citrus fruits and many other fruits and vegetables. Chronic vitamin C deficiency causes scurvy, which predominantly relates to abnormal collagen production.

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Nutritional intake can be subdivided into macronutrients and micronutrients. Macronutrients include carbohydrates, proteins and fats. These are consumed in relatively large amounts, primarily for their calorific value stored in their chemical bonds and as essential building blocks for cells and tissues. Micronutrients are required in much smaller quanties and comprise organic vitamins and inorganic minerals.

Vitamins are essential for normal growth and cellular metabolism, with many acting as essential co-factors for cellular enzymes to function. Vitamins the body cannot manufacture are classed as essential vitamins and must be acquired through the diet. A smaller number are non-essential because they can be synthesised directly by human cells. The major vitamin groups can be broadly subdivided into those that are water soluble and those that are fat soluble (Fig 1).

This series will examine the physiological roles of the major groups of vitamins and minerals, including the pathological effects of vitamin and mineral deficiencies and potential toxic effects of overdosing certain micronutrients. This first article describes the structure and function of vitamins A and C.

Vitamin A (retinol)

Although commonly known as retinol, vitamin A includes a large group of structurally related molecules, including retinol, retinoic acid, retinal and the carotenoids. Carotenoids are a group of yellow/orange/red-coloured vitamin A precursor (provitamin) molecules that include beta-carotene (Fig 2). Vitamin A is fat soluble and found preformed in many foods. Good sources include:

- Dairy products, such as milk, butter, cheese and yoghurts;
- Liver;
- Eggs;
- Oily fish;
- Foods fortified with vitamin A, such as many low-fat spreads.

The body can also synthesise vitamin A from beta-carotene. This is found in high

concentrations in many yellow, red and green vegetables (for example, spinach, carrots, sweet potatoes and red peppers) and yellow fruits (for example, apricots, papaya and mangos). The current daily recommended dietary allowance for vitamin A is 700µg for men and 600µg for women (NHS, 2020a). Physiological roles of vitamin A are discussed below.

Vision

Vitamin A is essential to the visual system as it is needed for the biosynthesis of light-sensitive pigments in the light-detecting cells of the retina. Humans have two major types of light-sensitive cells – rods and cones – which are classified according to their shape (Knight et al, 2022).

Rods

When light levels are low, human eyes are poor at detecting colour, but much better at detecting different light intensities (commonly known as monochromatic or black-and-white vision). Rhodopsin is a key light-sensitive pigment found in particularly high concentrations in the rods, which are responsible for monochromic vision. There are around 20 times more rods than cones in the human retina and these cells are incredibly sensitive, being capable of detecting a single photon of light (Krishnamoorthi et al, 2023); this makes them perfect for vision when light levels are low.

Vitamin A is continually transported in the blood to the retina; in the rods, it is converted into retinal, which combines with the protein opsin to form rhodopsin (Fig 3). This pigment is particularly effective at absorbing green/blue light, giving it a characteristic reddish/purple colour; hence, it is commonly called visual purple. When light focused on the retina is absorbed by rhodopsin, the retinal component changes shape (Fig 3). This configurational change causes the generation of an action potential (nerve impulse) that can then be relayed along the optic nerve to the visual cortex of the brain (Sajovic et al, 2022). The retinal and opsin components then separate and are recycled (Fig 3).

Cones

Cones are concentrated in the fovea centralis, the most sensitive region of the retina. There are three types according to the colour (wavelength) of light they detect, with red, green and blue cones present. As red, green and blue are the primary colours of light, these three cone types allow for the detection and perception of a broad spectrum of colours, which is often called

Fig 1. **Classification of vitamins**

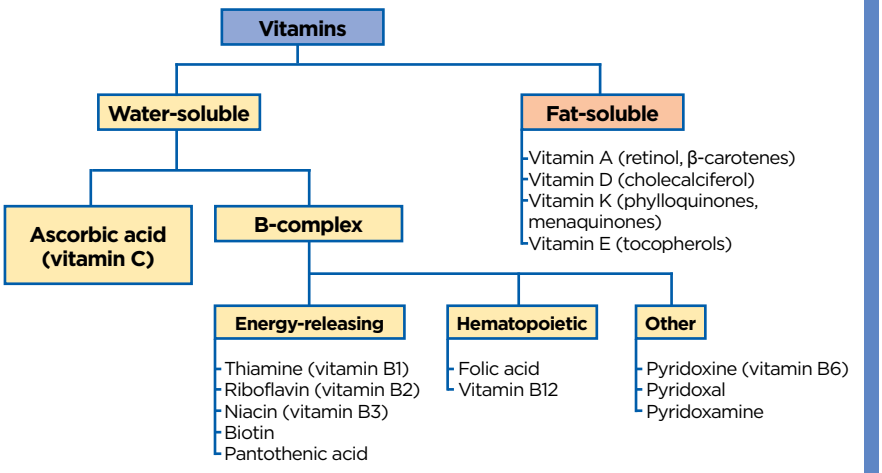


Fig 2. **Vitamin A and related molecules**

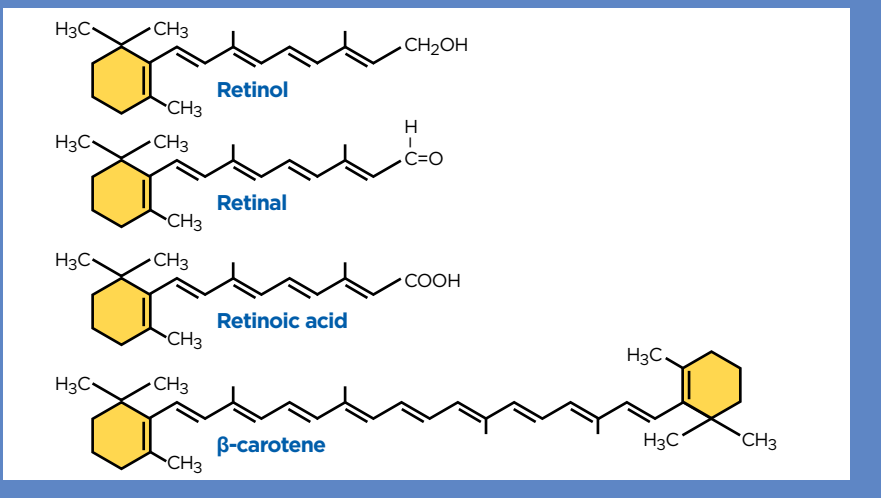
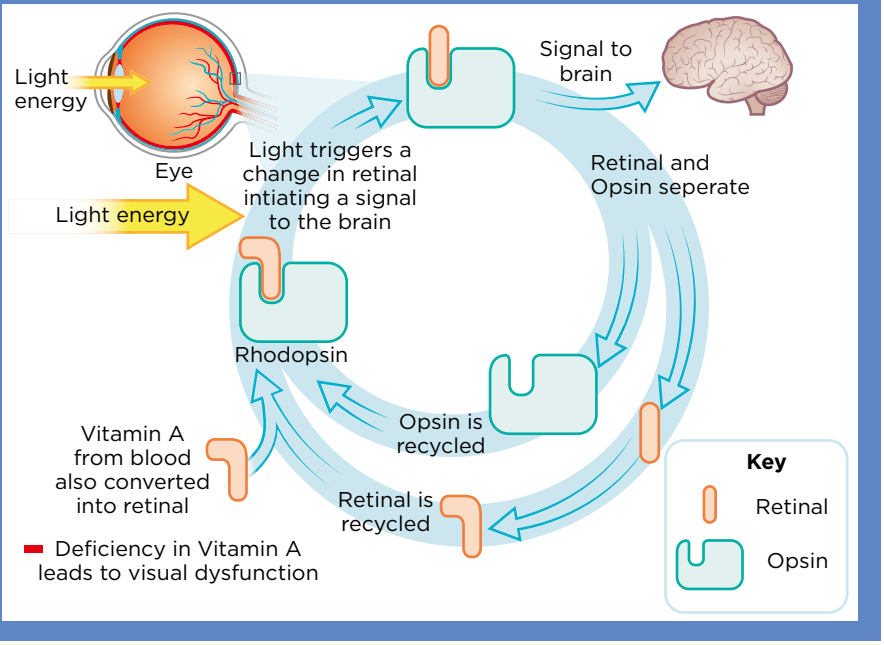


Fig 3. **Vitamin A and vision**



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trichromic colour vision (Krishnamoorthi et al, 2023).

Some people inherit defective genes on the X chromosome, which can result in colour blindness. Congenital colour blindness is much more common in males (8%) than females (0.4%) (Fareed et al, 2015). This is because females inherit two X chromosomes, so the effects of a defective gene on one X chromosome can be overridden by a healthy gene on the other. Males only have a single X chromosome, so cannot compensate in this way.

Cones contain photosensitive pigments that are structurally similar to rhodopsin; formerly known as iodopsins, these are now more commonly called photopsins or cone opsins. Like rhodopsin, the formation of cone opsins requires vitamin A. Humans have three major cone opsins in the retina, which can detect red, green and blue light, respectively.

Cones are far less sensitive than rods and typically require hundreds of photons of light to become activated (Krishnamoorthi et al, 2023). This is not usually an issue because high-resolution human colour vision generally relies on good lighting conditions. As with the rods, raw visual information from the cones relating to colour is relayed via the optic nerves to the visual cortex, situated in the occipital lobes at the back of the cerebral hemispheres. Here, visual information relayed from the rods and cones is processed and used to construct our visual interpretation of the world around us (Knight et al, 2022).

Night blindness and xerophthalmia due to vitamin A deficiency

Deficiency in the supply of vitamin A to the retina is associated with reduced biosynthesis of rhodopsin. This leads to poor light adaptation in darkened conditions, commonly called night blindness or nyctalopia. As vitamin A is also required for biosynthesis of cone opsins, deficiency can also cause poor daytime vision, with cone dysfunction causing poor colour perception and loss of visual acuity (Sajovic et al, 2022). These visual defects are potentially dangerous, being particularly associated with recurrent nighttime falls and difficulty with night driving (Mehra and Le, 2022).

As well as biosynthesis of photosensitive pigments, vitamin A is also essential to producing a healthy tear film, and deficiencies are associated with xerophthalmia (Greek for 'dry eye'). Although the aetiology of this is poorly understood, animal model experiments have shown an association between vitamin A deficiency and reduced flow of secretions from the tear-producing lacrimal glands (Conrady et al, 2016).

Vitamin A also ensures epithelial integrity of the conjunctival membranes covering the outer surface of the eyes and inner surfaces of the eyelids. It does this by maintaining the resident mucus-secreting goblet cells. It is also essential for regulating desquamation (loss) and keratinisation of cells in the cornea. Deficiencies in vitamin A can cause a softening of the cornea (corneal melt) and formation of corneal ulcers, which can lead to corneal perforation (Conrady et al, 2016).

QUICK FACT **25%** Prevalence of vitamin C deficiency among males in low income groups in the UK

Severe xerophthalmia is associated with vision loss and is the leading cause of preventable blindness in children in developing countries (Feroze and Kaufman, 2023). An estimated 254 million children worldwide have vitamin A deficiency and 2.8 million have xerophthalmia, causing around 350,000 children to become blind each year (Feroze and Kaufman, 2023).

A key early sign of vitamin A deficiency are Bitot's spots on the surface of the conjunctiva covering the cornea. These are regions of abnormal cell proliferation and keratinisation that can progress to corneal dryness (xerosis); this is usually reversible if detected early (Alashry and Morsy, 2021). Recommended treatment is 200,000 IU of vitamin A orally, repeated the following day, with a similar dose given several weeks later. Where necessary, topical treatment with preservative-free artificial tears and antibiotics can be given if bacterial infection is present (Feroze and Kaufman, 2023).

Immunological effects

Vitamin A is essential to human immunity and is often known as the "anti-infective vitamin" (Stephensen and Lietz, 2021). It has multiple roles in both non-specific and specific immune responses.

Epithelial integrity

The major mechanical barriers to infection are the skin covering most of the body's surface and the mucous membranes lining portions of the respiratory, digestive and reproductive tracts. Vitamin A is required to maintain the integrity and optimal function of the epithelial cells in these areas.

By binding to receptors inside keratinocytes (skin cells), vitamin A promotes their proliferation, strengthening the outer epidermal layer of the skin. It also reduces transepidermal water loss and is thought to protect collagen against degradation. For these reasons, vitamin A and its related molecules are often ingredients of topical anti-wrinkle and anti-ageing skin creams (Zasada and Budzisz, 2019). Vitamin A also promotes the production of antimicrobial peptides, such as resitins in human skin, which can kill bacteria at low concentrations (Roche and Harris-Tryon, 2021).

As vitamin A is essential to skin integrity, deficiency is associated with increased risk of skin infections and chronic skin diseases, such as acne vulgaris and psoriasis (Roche and Harris-Tryon, 2021).The drug isotretinoin, used to treat acne, is a vitamin A derivative that helps normalise follicular desquamation, reduces sebaceous gland activity, inhibits proliferation of the bacteria associated with acne (*Propionibacterium acnes*) and is anti-inflammatory. It has proven a highly effective acne treatment with a cure rate of around 85% at four months (Li et al, 2019). Despite conflicting reports on the association of this drug with depression, Li et al's (2019) meta-analysis indicated that its use in patients with acne was associated with a decreased risk of depression.

Leukocyte (white blood cell) function

Neutrophils are the most abundant leukocyte, accounting for up to 60% of the leukocyte population, and play a key role in non-specific immunity (Knight et al, 2020). They function as key phagocytic cells capable of trapping and killing pathogens on contact. Vitamin A is important for neutrophil differentiation, activation and the generation of neutrophil extracellular traps (Huang et al, 2018). These are thin strands of DNA that extend from the neutrophil and trap and immobilise pathogens (Knight et al, 2020). Vitamin A deficiency is associated with negative effects on phagocytic cells, involving impaired functioning of neutrophils and larger macrophages (Amimo et al, 2022)

Unlike non-specific immune responses, which target a wide range of potential pathogens, specific immune responses tend to target single pathogens. Lymphocytes, accounting for around 20-30% of the total leukocyte population, form the cornerstone of specific immunity (Nigam and Knight, 2020). There are two major populations of lymphocytes that are produced by the bone marrow:

- B-cells generate proteins termed antibodies. These Y-shaped molecules (also known as immunoglobulins) bind to and opsonise potential pathogens,

effectively marking out those pathogens for destruction by the immune system;
- T-cells originate from the red bone marrow (the tissue that makes red and white blood cells) and migrate to, and mature in, the thymus gland (hence the name). They have many functions, including their role as T-helper cells that assist the B-cells to produce antibodies; this is achieved via a cocktail of chemical signals, termed cytokines, which stimulate B-cell division and antibody production (Nigam and Knight, 2020).

Vitamin A plays a key role in differentiation and release of lymphocytes from the red bone marrow and also helps regulate lymphocyte function (Cañete et al, 2017). Animals that are fed diets rich in carotenoids (precursors to vitamin A) have greater levels of serum antibodies, thereby enhancing antibody-mediated immune responses (Huang et al, 2018). Vitamin A also appears to play a role in modulating the activity of T regulatory cells (T-regs), essential in maintaining immune tolerance and limiting damaging auto-immune reactions (Huang et al, 2018).

Due to the immense complexity of the immune system, the exact roles of vitamin A in immunity remain poorly understood; however, its reputation as an anti-infective vitamin appears well founded, with dietary vitamin A supplementation reducing morbidity and mortality in patients with measles, infantile diarrhoea, malaria, and hand, foot and mouth disease (Džopalić et al, 2021). Conversely, viral infections such as measles, and potentially Covid-19, appear more severe in patients who have vitamin A deficiency (Stephensen and Lietz, 2021).

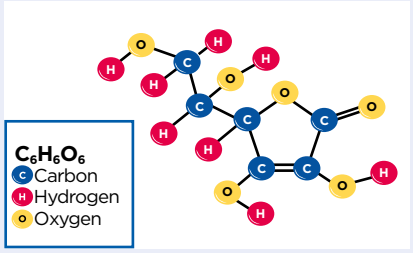
Erythropoiesis

Vitamin A appears to enhance erythropoiesis (erythrocyte or red blood cell production) by the red bone marrow. Although the mechanisms are unclear, they may be – at least partly – mediated by vitamin A helping to facilitate iron absorption. Treating iron-deficiency anaemia with iron supplements combined with vitamin A is more effective than treating it with either micronutrient alone (Cañete et al, 2017).

Bone physiology

Bone is a dynamic tissue continually formed by osteoblasts and broken down by osteoclasts. In health, these cells work at similar rates, maintaining bone density (Knight et al, 2020). Research on the effects of vitamin A supplementation on bone physiology is inconclusive – some studies have shown it increases bone density, others have shown a decrease with increased fracture risk and the remainder have shown no effect (Yee et al, 2021). Despite these inconsistencies, normal levels of both vitamin A and provitamin A are thought to act as osteoprotective agents, helping to maintain bone health. However, high doses of vitamin A appear associated with reduced bone density and increased fracture risk by inhibiting osteoblast activity (Yee et al, 2021).

Fig 4. **Vitamin C**



Male reproductive tract

For reasons not understood, normal levels of vitamin A seem necessary for healthy sperm production; deficiency is associated with impaired spermatogenesis and even testicular degeneration (Carazo et al, 2021).

Embryological development

Vitamin A is essential for normal embryonic development, because it is intimately involved in the cellular signaling associated with the formation of multiple organs, including the heart, eyes, brain, spinal cord and limbs (Berenguer and Duester, 2022).

Vitamin A as a teratogen

Teratogens are substances or ionising radiations that can interfere with normal embryonic development (following exposure during pregnancy), potentially leading to birth defects. A deficiency of vitamin A is also associated with birth defects because vitamin A is essential for normal embryonic development. Paradoxically, at high doses, vitamin A is a recognised teratogen, so consuming too much in pregnancy, particularly during the first 60 days, may also result in birth defects.

A daily intake of pre-formed vitamin A of >10,000 IU (3,000µg) is thought to be associated with teratogenicity, increasing the risk of miscarriage and congenital malformations involving the central nervous and cardiac systems (Bastos Maia et al, 2019). Pregnant women, who may well be concerned about their health and that of their unborn baby, may be tempted to take vitamin supplements; however, they are advised to avoid those containing >700µg of vitamin A and foods that are extremely rich in vitamin A, such as liver, liver pâté or fish liver oils (Royal College of Obstetricians and Gynaecologists, 2022).

Vitamin C (ascorbic acid)

Ascorbic acid, better known as vitamin C, is a water-soluble vitamin essential to many physiological processes. It is structurally related to glucose, with both molecules based around an asymmetrical group of six carbon atoms (C6H8O6) (Fig 4), and readily dissolves in water to form a weak organic acid (Yussif, 2019).

Unlike most plants and animals, humans cannot manufacture vitamin C, so it is designated an essential vitamin that must be obtained pre-formed through diet (Padayatty and Levine, 2016). Many people choose to boost their vitamin C levels by taking supplements. The daily recommended dietary allowance for vitamin C in adults is 40mg, which is easily achievable with a balanced diet (NHS, 2020b). Many fruits and vegetables are excellent sources of vitamin C, including:
- Citrus fruits, such as oranges, lemons and limes, and citrus fruit juices;
- Potatoes;
- Strawberries;
- Brussels sprouts;
- Broccoli;
- Blackcurrants;
- Peppers.

After absorption in the gut, vitamin C is distributed throughout the body dissolved in the plasma and is taken up by most tissues to varying degrees. Levels are particularly high in the adrenal glands, pituitary gland, retina and brain, but relatively low in the kidneys and muscles (Yussif, 2019).

Antioxidant effects

Free radicals are highly reactive atoms, ions or molecules with at least one unpaired electron. They are generated via normal metabolic processes, when leukocytes kill pathogens, or by exposure to environmental factors, including cigarette smoke, pollutants or ionising radiations.

Being highly reactive, free radicals can potentially inflict significant damage; exposure is associated with DNA mutation, malignancy, ageing and various autoimmune, cardiovascular and neurodegenerative diseases. Vitamin C is an effective antioxidant (reducing agent), and scavenges free radicals before they can inflict physical damage (Pehlivan, 2017).

Role in immunity and infection

Vitamin C enhances the activity of many leukocytes and accumulates in common leukocyte types, such as neutrophils and monocytes, at concentrations that are five to 100 times that of plasma (Carr and Maggini, 2017). Vitamin C enhances chemotaxis (in this case, the ability to move towards pathogens) in leukocytes. It also increases their phagocytic ability (trapping of pathogens) and enhances pathogen killing by increasing neutrophil production of free radicals, such as reactive oxygen species, which physically damage the pathogen (Carr and Maggini, 2017). Fortunately, the antioxidant properties of vitamin C help to limit the damage neutrophil-generated free radicals can inflict on both the neutrophil and the local tissues.

In lymphocytes, vitamin C increases cellular proliferation and antibody production, allowing more efficient opsonisation of pathogens for destruction; it also enhances the function of natural killer cells, which are involved in identifying and killing malignant cells (Yussif, 2019; Carr and Maggini, 2017).

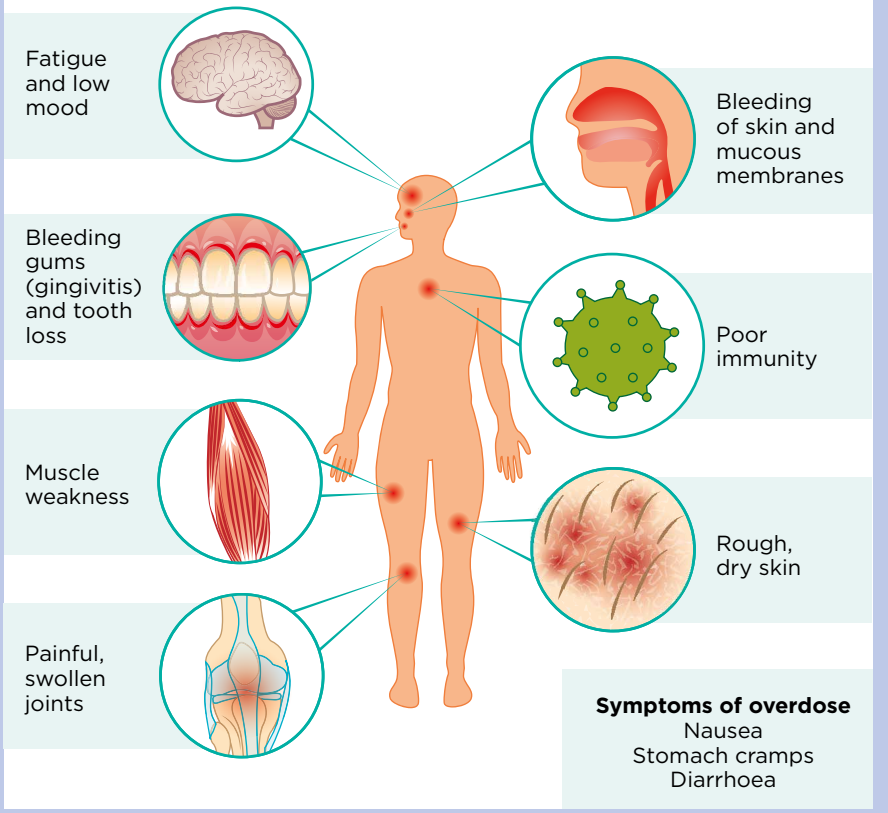
The role of vitamin C in bolstering immune function is supported by many studies that highlight its ability to alleviate or prevent a variety of infections caused by bacteria, viruses and protozoa (Hemilä, 2017). Vitamin C supplementation has been shown to halve the number of common colds in people who are physically active, decrease incidence of the common cold by 30% in British men and, when regularly administered, reduce the duration of the common cold (Hemilä, 2017). It may also be useful in helping to prevent pneumonia (Hemilä, 2017).

Kow et al's (2023) meta-analysis of 11 randomised controlled trials showed that vitamin C supplementation statistically significantly reduced mortality in patients who had severe Covid-19 infection.

Iron absorption

Anaemia (a reduced number of circulating red cells or haemoglobin within these cells) is thought to affect around 2 billion people worldwide, with iron-deficiency anaemia being the most common form (Skolmowska and Głąbska, 2022). Non-haem iron – that which is not associated with haemoglobin or myoglobin from animal sources – is the predominant form of dietary iron. This makes up around 85-90% of the total dietary intake (Skolmowska and Głąbska, 2022) but is absorbed less efficiently than haem iron. Vitamin C can enhance the absorption of non-haem iron in the gut by binding to it (chelating) and increasing its solubility at the wide pH range in the small intestine (Skolmowska and Głąbska 2022). Chronic vitamin C deficiency is associated with anaemia.

Fig 5. **Effects of vitamin C deficiency**



Collagen biosynthesis

Collagen is a key structural protein that is widespread in the human body and can be thought of as a 'general purpose' knitting protein. Its fibres act as binding and supporting structures in many organs and tissues, including bone, cartilage, muscle, tendons, ligaments, skin, teeth, gums, blood vessels, lungs, brain, the liver and the kidneys. Collagen fibres are primarily produced by fibroblast cells and 28 types of collagen have been identified (Boo, 2022). Vitamin C is essential for normal collagen production, acting as a cofactor for the enzymes prolyl hydroxylase and lysyl hydroxylase. These help to ensure the correct folding and stabilising of collagen into its characteristic triple helical structure (DePhillipo et al, 2018).

Vitamin C also increases fibroblast proliferation and collagen gene expression, and enhances collagen messenger ribonucleic acid (mRNA) levels, increasing the amount of collagen that is produced (Boo, 2022; Carr and Maggini, 2017). As vitamin C deficiency reduces collagen production and prevents it being correctly folded into its normal stable configuration, this can cause loss of tissue integrity and symptoms of scurvy, such as bleeding gums, fatigue and joint pain (Fig 5).

Skin integrity and wound healing

In health, the skin (or integument) accumulates vitamin C at a greater concentration than occurs in the blood, making it the most abundant integumentary antioxidant (Al-Niaimi and Chiang, 2017). This protects the skin against damaging free radicals. It also ensures healthy collagen generation. Collagen is a major part of the skin's dermal layer, supporting and anchoring elements, such as hair follicles, sebaceous glands, sweat glands, blood vessels and nerve endings (Knight et al, 2020).

Vitamin C deficiency reduces the skin's structural integrity, mainly due to abnormal collagen production (Boo, 2022). It is also associated with a thickening of the outer epidermal layer, which can lead to rough, dry skin – a common symptom of scurvy.

When the skin is damaged (for example, by a cut or graze), healing is triggered and fibroblasts divide and generate new collagen to knit the wound together; this is often observed as scar tissue at the wound

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site (Knight et al, 2020). Vitamin C deficiency is associated with poor wound healing, mainly due to abnormal collagen production and reduced fibroblast proliferation (Boo, 2022; Carr and Maggini, 2017).

Photo-ageing of the skin is multifaceted, but linked to solar radiation that triggers the formation of free radicals in the skin. Many topical skin creams incorporate vitamin C for its antioxidant properties. Such creams may also exert anti-ageing effects by enhancing collagen production; some studies show their use is associated with apparent anti-wrinkling effects and visible improvements in photo-ageing (Al-Niaimi and Chiang, 2017). Creams that contain vitamin C can also be used to reduce hyperpigmentation of the skin, such as melasma, which is common in pregnancy (Al-Niaimi and Chiang, 2017).

"Vitamin C is essential for normal collagen production"

Scurvy

Scurvy is a collection of diverse symptoms associated with chronic vitamin C deficiency; it was formerly common among sailors, until it was discovered that regularly eating citrus fruits was preventative and curative (Maxfield et al, 2023).

Vitamin C deficiency is common worldwide, particularly in developing nations – as an example, the prevalence of vitamin C deficiency in northern India is 73.9%, compared with 7.1% in the US (Callus et al, 2018). Although few studies relate to the UK, lower-income populations are thought to be particularly at risk – in these groups the prevalence of vitamin C deficiency in men and women has been estimated at 25% and 16% respectively (Callus et al 2018). Although not everyone with low levels of vitamin C will show symptoms of scurvy, it is estimated that stopping vitamin C intake will deplete the body's accumulated vitamin C pool in around 4-12 weeks (Maxfield et al, 2023).

Signs and symptoms of scurvy predominantly relate to abnormal collagen production. Collagen is an important component of blood vessels and significant deficiencies are associated with increased fragility of blood vessels. This can lead to easy bruising and bleeding (for example, the gums), which can contribute to anaemia (Nguyen, 2020). Key signs and symptoms of scurvy (shown in Fig 5) include:

- Gingivitis, bleeding gums, loose teeth or dental caries;
- Dry skin;
- Bleeding of the skin and mucous membranes;
- Anaemia;
- Increased risk of infection;
- Fatigue, malaise or depression.

Other associated symptoms include:

- Bruising;
- Coiled/corkscrew hair;
- Follicular hyperkeratosis (increased keratin in hair follicles);
- Joint stiffness/pain;
- Muscle weakness and aches/pains;
- Impaired wound healing.

Symptom progression can lead to fever, vasomotor instability, haemarthrosis (bleeding into joint spaces) and subperiosteal bleeding (bleeding under the outer bone sheaths). Inadequate treatment can lead to worsening of symptoms and eventually death (Callus et al, 2018). Treatment of scurvy includes increasing consumption of foods that are rich in vitamin C and, if required, use of high-dose vitamin C supplements (NHS, 2023).

Conclusion

Vitamins A and C are essential to many physiological processes and their deficiency can have a significantly negative impact on human health. **NT**

- The next article in the series examines the large family of water-soluble B vitamins.

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